have studied the effect of different surgical and mechanical procedures, and drugs, on the occurrence and severity of the edema. These studies are continuing and, therefore, only a brief summary of the results is given here.

Procedures useful in preventing or minimizing the edema were: (a) Intratracheal positive pressure; (b) bleeding during the infusion, and (c) denervation of the carotid sinus.

Useful drugs were: (a) Drugs inhibiting the sympathetic system (883 Fourneau,* ergotamine); (b) Curare; (c) Narcotics (barbital, phenobarbital, morphine, chloral); (d) Procaine (subcutaneous injections); (e) A combination of atropine and physostigmine.

Comment. A definitive interpretation of the results will be possible only after completion of the study. However, the experiments appear to show that stimulation of the cardiovascular receptors (chiefly those of the carotid sinus) has a prominent part in the genesis of our type of experimental pulmonary edema by increasing in a reflex way the permeability of the lung capillaries.

* 2-diethylamin-ethyl-1,4-benzodioxan is the formula of 883F.

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Experimental Alloxan Diabetes in Hooded Rats.

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Following the demonstration of Shaw Dunn and his collaborators[1,2] that alloxan, administred intravenously, produces rapid necrosis of the islets of Langerhans in rabbits, various investigators have observed the same effects on the islets and the development of persistent diabetes following parenteral injections of alloxan in rabbits,[3-6] white rats,[7,8] and dogs.[9,10] Gomori and Goldner[8] failed to produce these effects in 5 hooded rats given intraperitoneal injections of alloxan in doses of 200 mg per kg of body weight and, accordingly, they considered hooded rats resistant to alloxan.

On the contrary, we have found islet lesions and disturbances of blood sugar levels without exception in more than 60 hooded rats injected subcutaneously with alloxan (Eastman) in doses of 175 to 350 mg per kg of body weight. In these experiments a single injection of a 5% solution of alloxan was employed in each case. Blood sugar determinations were made by a modified Folin micro method as frequently as every 1 or 2 hours during the first 12 hours, every 3 to 6 hours up to 48 hours and at longer intervals thereafter. The animals either died, were killed when moribund or were sacrificed at desired intervals. Complete autopsies were performed in every instance and tissues appropriately fixed for histological staining with haematoxylin and eosin, Best's carmine stain for glycogen and Gomori's stain for granules in islet cells of the pancreas.

1 Dunn, J. S., Sheehan, H. L., and McLetchie, N. G. B., *Lancet*, 1943, **1**, 484.

2 Dunn, J. S., Kirkpatrick, J., McLetchie, N. G. B., and Telfer, S. V., *J. Path. and Bact.*, 1943, **55**, 245.

3 Bailey, C. C., and Bailey, O. T., *J. A. M. A.*, 1943, **122**, 1165.

4 Hughes, H., Ware, L. L., and Young, F. G., *Lancet*, 1944, **1**, 148.

5 Goldner, M. G., and Gomori, G., PROC. SOC. EXP. BIOL. AND MED., 1944, **55**, 73.

6 Hard, W. L., and Carr, C. J., PROC. SOC. EXP. BIOL. AND MED., 1944, **55**, 214.

7 Dunn, J. S., and McLetchie, N. G. B., *Lancet*, 1943, **2**, 384.

8 Gomori, G., and Goldner, M. G., PROC. SOC. EXP. BIOL. AND MED., 1943, **54**, 287.

9 Goldner, M. G., and Gomori, G., *Endocrinology*, 1943, **33**, 297.

10 Brunschwig, A., and Allen, J. G., *Cancer Research*, 1944, **4**, 45.

Within one hour after the injection of alloxan the blood sugar level had begun to rise from its normal average of about 100 mg % and at two hours reached a peak of from 130 to 240 mg %. Therefter the blood sugar fell to normal or below normal by the end of 4 to 6 hours and rose again above the normal level within 6 to 24 hours. Hypoglycemia did not always occur; the lowest blood sugar level recorded during this phase was 52 mg %. Hypoglycemic convulsions were not observed. Urine collected during the first 6 hours regularly showed a pink color, not due to haematuria or haemoglobinuria, but resembling closely the color that results when alloxan solution is allowed to evaporate in air. Glycosuria was present within the first 24 hours in all cases of marked hyperglycemia.

After the first 24 hours the results varied with the dosage of alloxan and apparently also with the individual susceptibility of the animals. Usually with the larger doses of alloxan (300 to 350 mg per kg) and sometimes with smaller doses, the blood sugar rose rapidly within 30 to 48 hours to values of 800 to 1450 mg % and death occurred within 36 to 96 hours in a state suggestive of diabetic coma accompanied by massive glycosuria and acetonuria. On the other hand, with smaller doses (175-200 mg per kg) and sometimes with larger doses, the blood sugar rose gradually within 2½ to 5 days to a peak of about 500 mg %. The animals survived for weeks or even months without treatment, with blood sugar levels of 300 to 500 mg%. These rats exhibited marked glycosuria (excreting as much as 5.5 g of sugar per day) as well as polyuria, polydypsia, polyphagia and progressive loss of weight when maintained on their ordinary diet of Purina Fox Chow without carbohydrate supplement.

The earliest histological examination of tissues was made one hour after injection of 350 mg per kg of alloxan and alterations were already discernible in some of the larger islets of Langerhans in the form of moderate nuclear pyknosis of a few of the central cells. During the next few hours, pyknosis of nuclei became more marked and extensive. The affected cells appeared markedly distended owing to great swelling of the cytoplasm; the cells became detached from one another and their normal cord-like arrangement was distorted. This stage was followed by fragmentation of nuclei and fading of nuclear staining with rupture of the cell membranes. By the end of 24 hours, as a result of complete disintegration of cells, the centres of many of the islets were occupied only by pale staining granular debris partly surrounded by clusters of surviving peripheral cells. The picture of more or less complete and widespread dissolution of islets was most conspicuous between 24 and 72 hours. Within the next 2 or 3 days there was a gradual condensation and disappearance of the necrotic debris with a corresponding collapse and shrinkage of the affected islets. Finally, although the general impression was one of paucity of islets in the histological sections, careful search revealed the presence of small solid clusters of surviving islet cells. The changes described were less extensive and developed more slowly with smaller doses of alloxan.

While the majority of the islet cells destroyed were beta cells, some of the more centrally placed alpha cells were also observed to be necrotic. The majority of the peripheral alpha cells evidently survived the injury and formed the greater part of the small islet cell clusters that remained to represent the original islets. In addition, however, some of the shrunken islets contained a few cells with clear agranular pale staining cytoplasm.

Although all previous investigators who have commented on the state of the acinar tissue of the pancreas following injections of alloxan have reported the absence of significant alterations, we have found in the first 24 hours after injection a striking increase in mitotic activity in the acinar cells. In sections of the pancreas from control animals, the most careful search revealed only rare mitotic figures in acinar cells, but beginning at 2 hours after injection of alloxan the number of mitotic figures was significantly increased. This increase continued, reaching a maximum at 17 hours when as many as 287

mitotic figures were counted in one section containing several small fragments of pancreatic tissue. Thereafter, the number of mitoses decreased to approximately normal rarity by the end of 24 hours. The distribution of acinar cells in mitosis appeared to be completely haphazard. The even smaller numbers of mitotic figures observed in the pancreatic ductular epithelium of control animals were not discernibly increased in the experimental animals. No mitotic figures were seen among islet cells at any time.

With the exception of slight degenerative changes in the convoluted tubules of the kidneys and the irregular occurrence of slight fatty metamorphosis of the liver, no significant alterations were observed in organs other than the pancreas, including the other endocrine organs. Histological alterations of the adrenal medulla similar to those described by Hard and Carr[6] were encountered irregularly in both experimental and control animals.

Sections of the liver from diabetic animals were found histologically to be lacking in glycogen. The heart muscle contained some stainable glycogen but this was not distinctly greater in quantity than normal. The deposition of glycogen in the renal tubular epithelium, especially of the loops of Henle, was satisfactorily demonstrated in several diabetic animals.

Summary. Alloxan administered to hooded rats in single subcutaneous injection in doses of 175 to 350 mg per kg of body weight regularly produced rapid selective necrosis of the islets of Langerhans and characteristic fluctuations of the blood sugar level. During the first 24 hours, irrespective of dosage, a blood sugar curve of typical form was obtained. Thereafter, following the higher doses of alloxan, the blood sugar rose rapidly to very high values and death occurred in a state resembling diabetic coma. With the lower doses employed the animals survived for periods up to several months with persistent diabetes. Histological alterations in the islets of Langerhans conformed to those described by previous investigators in white rats following alloxan. In addition, a great increase was observed in the activity of mitotic division in acinar cells of the pancreas during the first 24 hours after injection of alloxan.

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Transmission of Penicillin Through Human Placenta.*

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This study was undertaken to determine the existence of a placental barrier to penicillin.

Experimental. Four normal patients were selected while in active labor. Delivery was expected within 2 hours. Penicillin,† dissolved in normal saline, was administered intravenously. Ten cubic centimeters of saline were used irrespective of the dose administered. The calcium salt of penicillin was used in one case, the sodium salt in the remainder.

Samples of the maternal blood were taken for assay at intervals from the time of injection up to and including the time of delivery. At the time that the baby was separated from the placenta, placental cord blood was withdrawn into a sterile test tube. In one instance (Case 1) a pipette was inserted into the uterus following spontaneous expression of the placenta. Blood was aspirated from the uterus for assay. In Case 3 the amniotic sac was perforated about 5 minutes prior to delivery and amniotic fluid obtained for assay.

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† The penicillin used throughout this study was supplied through the kindness of Mr. John L. Smith, Chas. Pfizer & Co., Brooklyn, N. Y.